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ABSTRACT

Understanding potential drug interactions of multiple drug therapy influences the induction agents chosen for an individual patient. The use of muscle relaxants is a common aspect of modern anesthesia practice. Succinylcholine, a depolarizing agent, has been used since 1952 but due has numerous adverse side effects. Non-depolarizing neuromuscular blocking agents achieve the same efficacy as succinylcholine without the adverse effects. Rocuronium, an intermediate acting non-depolarizer, provides an alternative for intubation when succinylcholine is not recommended. Rapacuronium, approved in 1999, has a shorter onset and duration of action than rocuronium. The goal of this study was to determine whether the duration of action of rocuronium is affected by the prior administration of rapacuronium or succinylcholine. Quantitative data was obtained from 30 volunteers randomly placed in two groups. For induction, Group A received succinylcholine and Group B received rapacuronium. Both groups received rocuronium for maintenance. The Paragraph™ Nerve Stimulator was used to observe the neuromuscular response (return of the second twitch) during the first maintenance dose of rocuronium. An independent samples *t*-test found no statistically significant difference ($p = 0.111$) between the study groups. The mean time for return of the second twitch (in minutes) for Group A was shorter (26.87) than Group B (36.20). Although the data did not yield statistical significance, there may be clinical implications of the results observed in terms of cost and reversal time. The investigators note that rapacuronium was voluntarily taken out of the market as of April 2001 but this did not affect the data.

Key Words: **neuromuscular blockade rapacuronium rocuronium succinylcholine train of four**

THE EFFECT OF RAPACURONIUM OR SUCCINYLCHOLINE ON THE DURATION OF ACTION OF ROCURONIUM

by

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THESIS

Presented to the Graduate School of Nursing Faculty of

the Uniformed Services University of the Health

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MASTER OF SCIENCE

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October 2001

THE EFFECT OF RAPACURONIUM OR SUCCINYLCHOLINE ON THE DURATION OF ACTION OF ROCURONIUM

A Master's Thesis

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LIST OF FIGURES

LIST OF APPENDICES

ABSTRACT

Understanding potential drug interactions of multiple drug therapy influences the induction agents chosen for an individual patient. The use of muscle relaxants is a common aspect of modern anesthesia practice. Succinylcholine, a depolarizing agent, has been used since 1952 but due has numerous adverse side effects. Non-depolarizing neuromuscular blocking agents achieve the same efficacy as succinylcholine without the adverse effects. Rocuronium, an intermediate acting non-depolarizer, provides an alternative for intubation when succinylcholine is not recommended. Rapacuronium, approved in 1999, has a shorter onset and duration of action than rocuronium. The goal of this study was to determine whether the duration of action of rocuronium is affected by the prior administration of rapacuronium or succinylcholine. Quantitative data was obtained from 30 volunteers randomly placed in two groups. For induction, Group A received succinylcholine and Group B received rapacuronium. Both groups received rocuronium for maintenance. The Paragraph™ Nerve Stimulator was used to observe the neuromuscular response (return of the second twitch) during the first maintenance dose of rocuronium. An independent samples *t*-test found no statistically significant difference ($p = 0.111$) between the study groups. The mean time for return of the second twitch (in minutes) for Group A was shorter (26.87) than Group B (36.20). Although the data did not yield statistical significance, there may be clinical implications of the results observed in terms of cost and reversal time. The investigators note that rapacuronium was voluntarily taken out of the market as of April 2001 but this did not affect the data.

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TABLE OF CONTENTS

CHAPTER I: INTRODUCTION

Background

Clinical muscle relaxation was first used in 1942 with the introduction of d-tubocurarine (dTc); however, patients receiving this drug were found to have a six-fold increase in mortality rate. Today, with the discovery and understanding of ventilatory support, and careful monitoring, the use of neuromuscular-blocking agents has been refined, and their use is now a common aspect of modern anesthesia practice (Savarese, Caldwell, Lien, & Miller, 2000).

Succinylcholine has been used since 1952, and is the only depolarizing neuromuscular-blocking agent used clinically. For almost 50 years, its popularity has been unsurpassed. Succinylcholine at 0.5 – 1.0 mg/kg has a fast onset of action (within one minute) and short duration of action (three to five minutes). These properties made succinylcholine the drug of choice for providing skeletal muscle relaxation for rapid sequence intubation (Savarese et al., 2000). Unfortunately, patients receiving succinylcholine have had numerous adverse reactions that include, but are not limited to, cardiac dysrhythmias, hyperkalemia, masseter spasm, myalgia, and malignant hyperthermia. Due to its side effects, succinylcholine is contraindicated in certain clinical situations, such as increased intracranial pressure or penetrating eye injury (Durant & Katz, 1982).

As a result of these adverse reactions, the search for succinylcholine replacement has been ongoing. The replacement drug would have to provide the same efficacy as succinylcholine with minimal side effects. Non-depolarizing neuromuscular blocking agents are thought to achieve the same efficacy as succinylcholine without as many

adverse effects as succhinylcholine. Rapacuronium bromide (Org 9487, Raplon ™) or rapacuronium, a nondepolarizing neuromuscular-blocking agent, newly approved by the Food and Drug Administration, may be such a replacement. As a 16-N-allyl-17-Greek beta-propionate analogue of vecuronium, a long-acting nondepolarizing agent, it has a low potency (ED_{95} 1.15 mg/kg), fast onset, and short-to-intermediate duration of action depending on the dosage. Time to maximum depression of the train-of-four (TOF) twitch response is 62 seconds at the laryngeal muscles and 96 seconds at the adductor pollicis muscle. Similar to succinylcholine at 1 mg/kg, rapacuronium produces good-to-excellent intubating conditions at 60 seconds when given in 1.5 – 2.0 mg/kg doses. It becomes an intermediate-duration muscle relaxant when given as a continuous infusion over an hour. This may be due to the accumulation of the more potent and longer-acting 3-hydroxy metabolite. Controlled pre-marketing clinical trials by the manufacturer, Organon Incorporated, showed hypotension (5.2%) to be the most common adverse effect, followed by tachycardia (3.2%), bronchospams (3.2%), and bradycardia (1.5%) in 2036 subjects (Organon, 1999). Although there is little clinical experience with rapacuronium, early studies indicate that it may be suitable for procedures lasting less than 60 minutes and for rapid-sequence tracheal intubation, thus it may be a suitable alternative to succinylcholine (Savarese et al., 2000).

Rocuronium bromide (rocuronium) is an aminosteriod, nondepolarizing neuromuscular blocking agent. Its rapid onset of action provides an alternative for intubation when succinylcholine is not advantageous (Stoelting, 1999). Favorable conditions for tracheal intubation can be reached in 60-120 seconds. The duration of action, 20 - 35 minutes, classifies this nondepolarizer as an intermediate acting agent.

Appropriate dosing for tracheal intubation of rocuronium is 0.9mg -- 1.2mg/kg (Savarese et al., 2000), a maintenance dose of 0.3 – 1.2 mg/kg is considered appropriate (Stoelting, 1999).

Rocuronium is a derivative of vecuronium; its site of action compares to rapacuronium. Rocuronium and rapacuronium are competitive inhibitors of acetylcholine at the cholinergic receptors on the motor end plate. The low potency of rocuronium allows a greater number of molecules to saturate the nicotinic receptors faster than vecuronium, thus explaining the rapid onset of action (Savarese et al., 2000). Cardiovascular effects are minimal and there is no significant histamine release, a characteristic that is comparable to other nondepolarizers. Savarese et al. reported incidences of slight to moderate increases in heart rate with doses of 0.9mg -- 1.2mg/kg. Heier and Caldwell (2000) explored doses of rocuronium as high as 2.0mg/kg and found no dose related changes in heart rate or blood pressure.

The major site for metabolism for rocuronium is the liver. Approximately 10% of rocuronium is excreted by the kidneys with no significant active metabolites. One metabolite of rocuronium is 17-desacetylrocuronium, which is approximately 5% as potent as the parent compound (Lewis, Santucci, Normoyle, & Rothenberg, 1999). Factors that have been implicated in affecting the pharmacokinetics and pharmacodynamics of rocuronium include age, weight, use of inhaled anesthetics, hepatic and renal insufficiency, and hypothermia.

Induction and maintenance of anesthesia requires multiple drug therapy that can potentiate the risk of drug interactions. Drug interactions include additive effects, synergistic effects, antagonism, and cross-tolerance (Stoelting, 1999). An understanding

of potential interactions influences the combination of drugs chosen for an individual patient. Stoelting defines additive effects as the total sum of the effects produced by the individual drugs when used in combination, synergism as a greater effect than the sum of the individual drugs combined, and antagonism as a lesser effect achieved when drugs are combined.

Drug interactions that may potentiate the effects of rocuronium include, but are not limited to, aminoglycosides, calcium channel blockers, local anesthetics, inhaled anesthetics, and other neuromuscular blocking agents. Antagonism may occur with the use of calcium, carbamazepine, phenytoin, theophylline, caffeine, and anticholinesterases (Stoelting, 1999). Potential drug interactions of rapacuronium are not well known due to its recent availability; more research is needed to ensure a more complete understanding of the drug.

Nursing Implications

In the United States, nurse anesthetists, either as sole providers or in collaboration with an anesthesiologist, provide 65% of anesthetics delivered (American Association of Nurse Anesthetists , 2000). All anesthesia providers should be aware of the pharmacokinetics and pharmacodynamics of the drugs they administer. A major concern of anesthetists is the use of succinylcholine during difficult endotracheal intubations, using a rapid-sequence technique. Although it has been shown to be effective for rapid-sequence intubation, it is not without risks, and is contraindicated in certain patient populations. The search for agents other than succinylcholine is overdue. To provide our patients with the best care possible, a neuromuscular blocking agent with a short duration

of action or one which can be reversed early is warranted (Wierda, van den Broek, Proost, Verbaan, & Hennis, 1993).

With a plethora of new medications coming out in the market, the potential for drug-to-drug adverse interactions is tremendous. The importance of understanding the pharmacological principles and drugs used in anesthetic practice cannot be overemphasized. Exploring benefits and risks provide for a greater understanding and applicability for use. Nurses must be able to contribute to the research of medications used in practice to enhance the safety of their use and to provide for a safer patient environment.

Purpose of the Study

The purpose of this study was to determine how rapacuronium and succinylcholine effect the duration of action of rocuronium.

Research Question

Did the duration of action of rocuronium differ between patients given an intubating dose of rapacuronium versus an intubating dose of succhinylcholine?

Theoretical Framework

A pharmacological model was used to explain the combined actions of the neuromuscular blocking agents used in this study. The results observed when combining succinylcholine with rocuronium, and rapacuronium with rocuronium, is dependent on pharmacological characteristics. Succinylcholine mimics the actions of acetylcholine by occupying both alpha subunits of the nicotinic cholinergic receptors, generating an action potential at the motor end-plate. After generating an action potential, the sodium channels close and cannot open; a condition which is irreversible, until the

succinylcholine has been metabolized by pseudocholinesterase (Morgan & Mikhail, 1996). Rapacuronium and rocuronium are competitive, nondepolarizing neuromuscular blocking agents. The mechanism of action for rapacuronium and rocuronium are the same; they compete with acetylcholine at the motor end-plate and block acetylcholine from occupying the receptors. The sodium channels are prevented from opening, and therefore, an action potential is not generated. The actions of rapacuronium and rocuronium can be reversed by anti-cholinesterase drugs. Rapacuronium has a longer duration of action when compared to succinylcholine (Savarese et al., 2000) which may suggest the combination of rapacuronium and rocuronium will produce a longer duration of action when compared to succinylcholine and rocuronium. The mechanism of action for succinylcholine, however, is different than rapacuronium. Savarese et al. suggest that the use of a short-acting nondepolarizer, such as rapacuronium, followed by a maintenance dose of an intermediate-acting nondepolarizer, such as rocuronium, will produce a shorter duration of action of the first maintenance dose. The shorter duration of action is due to kinetics and the three half-lives required before the clinician sees a longer duration of action of the maintenance dose. This study compared the effects of rapacuronium and succinylcholine on the duration of action of rocuronium. The pharmocokinetics, to include the different mechanisms of action, for rapacuronium and succinylcholine may explain the anticipated results.

Results were observed and recorded using peripheral nerve stimulation. Peripheral nerve stimulation allows conclusions to be drawn regarding depth and recovery of neuromuscular blockade and is the standard of care when neuromuscular blocking agents are administered. The use of peripheral nerve stimulation is a physical finding observed

as an electrical stimulus to a chosen nerve. The Paragraph™ Nerve Stimulator was the tool used for observation.

Conceptual Definitions

1. American Society of Anesthesiologists Classification: a physical status classification assigned to surgical patients according to the following criteria:

ASA class I: healthy patient;

ASA class II: patient with mild systemic disease;

ASA class III: patient with severe systemic disease, but not incapacitated;

ASA class IV: an incapacitated patient with severe systemic disease

(Keglovitz & Kraft, 1997).

2. Depolarizing neuromuscular blocking agent: attaches to the membrane receptor instead of acetylcholine and mimics its actions at the neuromuscular junction by depolarizing the membrane (Stoelting, 1999).

3. Nondepolarizing neuromuscular blocking agent: competes with acetylcholine at the membrane receptor, blocking its action. Drug molecules must occupy greater than 70% of the receptors in order to prevent neuromuscular transmission. The actions of nondepolarizers can be reversed by the use of anticholinesterase agents (Stoelting, 1999).

4. Peripheral nerve stimulation: used as a method for evaluation of neuromuscular blockade. It involves the electrical stimulation of a chosen peripheral nerve to judge depth of blockade, need for titration of the neuromuscular blocking agent, and recovery at the end of the surgical procedure (Stoelting & Miller, 1994).

5. Single twitch: a pattern for stimulation that involves one electrical stimulus provided to a peripheral nerve (Stoelting & Miller, 1994).

6. Train of Four: a pattern for stimulation that involves four electrical stimuli provided to a peripheral nerve. Nondepolarizing agents produce a pattern termed fade. The response to the electrical stimuli decreases with successive stimulation due to the depletion of acetylcholine at the receptors (Stoelting & Miller, 1994). For the purpose of this paper, train of four are referred to as TOF.

Operational Definitions

1. Paragraph™ Nerve Stimulator: Instrument used to provide electrical stimulus to selected peripheral nerve; quantitatively monitors neuromuscular blockade; measures single twitch, TOF, double burst, and tetany (Stoelting & Miller, 1994).
2. Rocuronium: FDA approved nondepolarizing neuromuscular blocking agent; intermediate acting; used for induction and maintenance of anesthesia (Savarese et al., 2000).
3. Rapacuronium: Food and Drug Administration (FDA) approved nondepolarizing neuromuscular blocking agent; short-to-intermediate acting; used for induction of anesthesia; minimal clinical experience regarding maintenance dosing at this time (Savarese et al., 2000).

Assumption

Peripheral™ nerve stimulators were in proper working condition to monitor TOF accurately. The electrode monitor is attached to the patient and the nerve was stimulated prior to the administration of the muscle relaxant. If difficulty was encountered while attempting to stimulate the nerve or a large difference was noted between the set current and the current delivered, the investigators would run the built in diagnostics program.

Limitations

1. The study was limited to healthy, ASA I and II, adult volunteers receiving general endotracheal anesthesia for surgery. This may limit the ability to generalize results beyond the sample studied.

2. Only one clinical site was sampled. This also may limit the generalizability of the results.

Summary

Succinylcholine is a staple neuromuscular blocking agent used for intubation while rapacuronium is a new non-depolarizing neuromuscular blocking agent. The mechanism of action differs between these two drugs. Succinylcholine may not be the drug of choice in certain clinical situations due to undesirable side effects. Rapacuronium may be better but it has had minimal clinical exposure. This study compared the duration of action of rocuronium between patients given an intubating dose of succinylcholine versus an intubating dose of rapacuronium.

CHAPTER II: REVIEW OF THE LITERATURE

Introduction

Rapacuronium is a new nondepolarizing neuromuscular blocking agent. As an analogue of vecuronium, it has a low potency (ED_{95} 1.15 mg/kg), fast onset, and short-to-intermediate duration of action depending on the dosage. Rapacuronium has a time to maximum depression of TOF twitch response of 1.5 – 2.0 mg/kg similar to succinylcholine 1.0 mg./kg to the adductor pollicis muscle. Rapacuronium in doses of 1.5 – 2.0 mg/kg produces good intubating conditions at one minute, similar to succinylcholine. Rapacuronium's clinical duration of action (recovery to 25% twitch height) are about 15 to 20 minutes and 95 percent twitch recovery (ED_{95}) occurs in 25 to 30 minutes. The lower range of duration is achieved after doses of 1.5 mg/kg with higher duration after doses of 2.0 – 2.5 mg/kg (Savarese et al. 2000).

Rapacuronium is partially deacetylated at the three-position and excreted in the bile and urine as the parent compound (Org 9487), or the more active 3-desacetyl metabolite (Org 9488). The cumulative effect results in longer duration of action and slower recovery with periods of infusion of greater than 30 minutes or after repeated dosages. With continued infusion of rapacuronium for an hour, the time to recovery increases to that of an intermediate-duration relaxant. This observation may be due to the accumulation of the metabolite, which is more potent and longer acting than the parent compound (van den Broek, Wierda, Smeulers, & Proost, 1994).

According to Wierda et al. (1993), when difficult endotracheal intubation is anticipated, a nondepolarizing muscle relaxant is preferable due to masseter spasm induced by depolarizing agents. A short duration of neuromuscular blockade is required,

either by a short intrinsic duration, or by early reversibility in case of failed endotracheal intubation.

Neuromuscular blockade level can be tested by using a nerve stimulator. If all TOF responses are visible or palpable, relaxation is inadequate. If one or two responses are visible or palpable, relaxation is sufficient for an abdominal surgery under adequate depth of anesthesia. If only one twitch is visible or palpable, relaxation should be deep enough to allow intubation of the trachea under already established general anesthesia. If anesthesia is too light, relaxation may prove inadequate even if monitor indicators seem appropriate (Stoelting, 1999).

There has been little clinical experience with rapacuronium, however, it may be suitable for tracheal intubation and procedures lasting less than 60 minutes. It may also serve as an acceptable alternative to succinylcholine for emergent intubation of the trachea (Savarese et al., 2000).

A solid understanding of rapacuronium's pharmacodynamics and pharmacokinetics is important to the interpretation of the results that will be gathered in the course of this research. The review of the literature synthesizes previous research findings with regard to Rapacuronium's mechanism of action, advantages of rapid onset, ability to affect the laryngeal muscles by monitoring neuromuscular blockade, and appropriate dosages for desired results. A comparison to other neuromuscular blocking agents will also be explored.

Pharmacodynamics and Pharmacokinetics

van den Broek and colleagues (1994) evaluated the pharmacodynamic and pharmacokinetic effects of rapacuronium. Percent of blockade and plasma

concentrations of the neuromuscular blocking agent were used for interpretation. All patients were American Society of Anesthesiologist (ASA) class I and II, and ages ranging from 18 – 65 years. The study population consisted of ten patients, nine males and one female. No other exclusion criteria were discussed. Each patient received a premedication of midazolam. Induction agents consisted of fentanyl and propofol. Isoflurane and a mixture of nitrous oxide and oxygen were used for maintenance of anesthesia. Care was taken to maintain consistent partial pressure carbon dioxide (pCO2) and temperature.

Neuromuscular activity was monitored at the adductor pollicis muscle using single twitch and TOF ratio. An intubating dose of 1.5mg/kg of rapacuronium was administered to all patients within a ten-second time period via an intravenous line in the foot. When a 25% single twitch return was obtained, a continuous infusion was begun at 5mg/kg/hr. After initiation of the infusion, correction in dosages were made to ensure 75 – 85% blockade at the adductor pollicis. Venous blood samples were collected to measure plasma concentration of rapacuronium and its metabolite, 3-OHrapacuronium. Samples were drawn prior to the intubating dose, and at 10-minute intervals during infusion. Samples also were drawn at 2, 5, 10, 20, 40, 60, 120, 180, and 240 minutes post-infusion. Sodium dihydrogen phosphate was added to prevent degradation of rapacuronium. Urine samples were collected via catheterization at 8 and 24 hours post-infusion. Five of the patients recovered spontaneously, and the other five were given neostigmine, an anticholinesterase agent, for reversal of neuromuscular blockade (van den Broek et al., 1994).

Results were displayed by the use of MULTIFIT, a computer program providing linear least square regression analysis. No information was provided regarding confidence intervals (CI) or *p* values. One minute after the intubating dose was given, 71 +/- 30 % blockade was noted. The onset time to maximum block of 99% was 1.9 +/- 0.5 minutes. A mean continuous infusion of 3.4 +/- 1.0 mg/kg/hr was required for maintenance. The 15 minutes prior to termination of anesthesia required a reduced dose of 2.5 +/- 1.1 mg/kg/hr to provide 75-85% blockade (van den Broek et al., 1994)

Plasma concentrations of rapacuronium and its metabolite were plotted as concentration versus time. A drastic reduction in plasma levels occurred upon discontinuance of infusion. The 3-OH metabolite's concentration was much lower than its parent compound and its clearance was slower. The largest excretion of rapacuronium via urine occurred within the first eight hours. Most noted was recovery time difference for patients given rapacuronium as an infusion versus a single intubating dose. Recovery to 25% single twitch was 35.2 minutes post-infusion. A single, intubating dose recovery was documented at a mean of 16.1 minutes. van den Broek et al. (1994) concluded that rapacuronium, when used as an infusion, changes from a short acting to an intermediate acting neuromuscular blocking agent.

Wright, Brown, Lau, and Fisher (1999) studied how rapacuronium differed in its course of action at the laryngeal adductor muscles and at the adductor pollicis muscle. The purpose of this study was three-fold: (a) to determine if pharmacokinetic or pharmacodynamic characteristics can explain the rapid onset and recovery of rapacuronium, (b) to determine if differences between pharmacodynamic characteristics of rapacuronium and other nondepolarizing muscle relaxants can be compared using

laryngeal adductor muscles versus adductor pollicis muscle, and (c) to find whether venous rather than arterial concentrations can determine levels of rapacuronium in the 20-minute period after its administration.

Ten healthy ASA physical status I volunteers, ranging in age between 20 to 42 years old, underwent anesthesia without surgery. Standard anesthesia protocol was administered. After induction with Fentanyl and Propofol, a single five-second, 50 Hertz tetanic stimulus was applied to the ulnar nerve, followed by a TOF stimuli every 12 seconds. Adductor pollicis muscle twitch response was measured with calibrated force displacement transducer. TOF stimuli applied to the larynx via surface electrodes over the cricoid notch and forehead was measured via airway pressure changes. The first twitch response of each TOF (T_1) was stable for more than 15 minutes after rapacuronium was administered. Arterial blood (5 ml) was sampled at 0.5, 1, 2, 4, 6, 8, 10, and 20 minutes after rapacuronium administration. Venous blood was sampled before and at 3, 7, 10, 20, 30, 45, 60, 75, 90, and 120 minutes after rapacuronium administration (Wright et al., 1999).

According to the Hill Equation 1, (small gamma, Greek: the factor governing sigmoidicity of the concentration-effect relation and effective concentration of muscle relaxant depressing twitch tension by 50 percent at the effect site), twitch depression for each muscle group was assumed to relate to the effective concentration of muscle relaxant at the effect site. The values obtained after complete recovery of neuromuscular function were presented as the mean +/- Standard Deviation (SD); Student's *t*-test was used to compare mean values for muscle groups (Wright et al., 1999).

Two volunteers experienced 92% and 94% depression at laryngeal adductor muscle while the remaining eight had more than a 95% or greater depression at the laryngeal muscle, and a 100% depression at the adductor pollicis muscle. Laryngeal adductor muscles times to maximum depression and 10% recovery of T_1 were faster than at the adductor pollicis muscle. The time to 25% recovery of adductor pollicis twitch tension after rapacuronium administration was only slightly longer than after succinylcholine (8 +/- 2 minutes). Results displayed an onset of action that was faster and a duration that was shorter at the laryngeal muscles in comparison to the adductor pollicis. This more rapid equilibration correlates with the low potency of rapacuronium and suggests that limited partitioning between plasma and the effect site facilitates onset. No significant time difference was noted between the adductor pollicis or laryngeal muscles in reference to neuromuscular activity recovery. Minimal differences between arterial and venous drug-plasma levels were noted. The steady state rapacuronium plasma concentration that depressed twitch tension by 50% and the Hill factor were similar for the two muscles. In one patient, venous concentrations were slightly less than arterial concentrations, and could not be explained. Arterial and venous concentrations of rapacuronium were nearly identical in the rest of the patients. The time to complete depression of the adductor pollicis and the time to maximal depression of the laryngeal muscles after administration of 1.5 mg/kg rapacuronium were comparable to those observed for 1 mg/kg succinylcholine (Wright et al., 1999).

In an attempt to explain the rapid onset of rapacuronium, a comparison of the rate constant for the equilibration of the plasma level and effect site (keo) was made. A large keo was calculated due to the rapidly falling plasma concentrations post-administration;

this potentially explains its quick on/quick off characteristic. Wright et al. (1999) propose this finding is in contrast to previous data supporting resistance of the laryngeal muscles with the use of other steroidal nondepolarizing agents. Their study further suggests that the rapid time course of rapacuronium rival that of succinylcholine in facilitating tracheal intubation.

An advantage of the steroidal nondepolarizing agents is the lack of histamine release. This class has been shown to exhibit a greater vagolytic property instead of histamine side effects (Savarese et al., 2000). Levy et al. (1999) explored histamine release associated with rapacuronium, a study that involved 45 patients, ranging in age from 18-75 years, who were categorized as ASA class II or III. Patients with significant renal, hepatic, or neuromuscular disorders were excluded. Those on prescription histamine blockers, had significant allergy problems, or were greater than 30% above their ideal body weight also were excluded. All patients received diazepam orally and had a radial arterial line placed.

Results of plasma histamine levels recorded prior to administration of rapacuronium were considered not significant (Levy et al., 1994). Plasma histamine levels of 1.0 ng/ml or greater were considered significant. Levy et al. also noted that histamine levels of greater than 2ng/ml were required to contribute to significant cardiac effects. Five patients (one receiving 1mg/kg, one receiving 2mg/kg, and three receiving 3mg/kg group), displayed histamine levels greater than 1ng/ml. Two of the five patients in the 3mg/kg group experienced increased levels by 10 fold at one minute post-administration. The greatest increase in histamine plasma concentration occurred one minute post-administration, however, there was no direct correlation between the histamine levels and

hemodynamic changes. Seven patients did experience bronchospasm, but none were in the group with significant histamine levels. The authors concluded that rapacuronium does not contribute to a clinically significant histamine release.

Dose Ranging

Debaene, Liutaud, Billard, and Meistelman (1997) completed a clinical investigation to compare the neuromuscular blocking onset, peak, and duration of rapacuronium. Thirty ASA class I and II patients, between the ages of 18 – 65, undergoing peripheral procedures were assessed. Patients with cardiovascular, hepatic, renal, and respiratory disorders were excluded. Individuals with an abnormal upper airway, prior head and neck surgeries, a deviation by more than 20% of their ideal body weight, and on medications that could affect neuromuscular transmission also were excluded.

Induction included propofol and fentanyl, with no neuromuscular relaxant prior to intubation. The adductor pollicis was monitored, and measurement of the force of contraction was recorded. Laryngeal adductor muscle activity was monitored by measuring pressure changes of the inflatable cuff. Nitrous oxide and halogenated agents were avoided because of their ability to potentially affect the endotracheal cuff pressure. The cuff pressure was set initially at 10 –12mmHg and CO2 end-tidal tension was maintained between 30 – 40mmHg. TOF stimulation was utilized. Patients, randomly grouped in equal numbers, received either 0.75mg, 1.5mg, or 2.0mg/kg of rapacuronium intravenously (Debaene et al., 1997).

The Debaene et al. (1997) results were recorded in relation to the differing dosages given. The findings using a Student's *t*-test ($p < 0.001$) indicated the onset of action of rapacuronium was faster at the laryngeal adductors than at the adductor pollicis. The

duration of action also was shorter at the laryngeal adductors. Patients receiving 0.75mg, 1.5mg, and 2.0mg/kg, experienced an onset time of block of 62 seconds (+/- 16), 16 seconds (+/- 13), and 52 seconds (+/- 14), respectively. However, a greater range of onset time was recorded at the adductor pollicis, 126 seconds (+/- 33), 96 seconds (+/- 20), and 82 seconds (+/- 21), respectively. A 95% confidence interval was used for interpretation of the data. Debaene et al. deduced that maximum block at the laryngeal adductors was not as dependent on the dose received as observed at the adductor pollicis.

Kahwaji et al. (1997) provided another look at the potential dose ranging dependency of rapacuronium. Their goal was to find the most favorable dosage of rapacuronium for ideal intubating conditions. This was a multicenter, randomized study involving a total of 181 patients classified as ASA class I, II, and III. Patients were divided into two age related groups. The younger adult group, ages 19 – 64 years, accounted for 120 subjects. The other group of 61 patients ranged in ages between 65 – 85 years. Patients were excluded if there were anticipated difficulties in tracheal intubation during the preoperative assessment. Those with no significant neurological, renal, or hepatic disease, and anyone receiving medications that could alter neuromuscular response also were excluded.

Induction agents used for all patients included fentanyl and thiopental. Maintenance of anesthesia was controlled with a N2O/O2 mixture and propofol. The use of volatile anesthetics was avoided prior to induction, and standard anesthesia induction protocol was used. Neuromuscular monitoring by electromyography was performed using a Puritan Bennett Datex Relaxograph to record response of adductor pollicis muscle to TOF supermaximal stimulation of ulnar nerve at ten-second intervals. Monitoring was

started immediately after induction and within 30 seconds of injection by one of the five doses of rapacuronium (0.5, 1.0, 1.5, 2.0, 2.5 mg/kg) or a placebo (normal saline). Intubation attempt was made one minute after muscle relaxant was given. A blind observer assessed intubating conditions using a four-point scale (impossible, poor, good, excellent). If intubation was impossible, a second attempt was made 90 seconds after rapacuronium; and if, after, the second attempt failed, vecuronium (0.1 mg/kg) or rocuronium (0.6 mg/kg) was given to facilitate intubation. Maximum block, clinical duration (time to 25% T1 recovery), and recovery (TOF $\geq$ 0.7) were measured. Statistical comparisons of the intensity and duration of the neuromuscular block in adults and elderly patients and the demographic data were made using analysis of variance (ANOVA) (Kahwaji et al., 1997).

Before the administration of rapacuronium, three elderly patients were excluded from the study due to contraindicated drug administration, equipment failure, or clinical decision. Although 10 patients had protocol deviations ranging from incorrect dosage, allocation to incorrect age group, or anesthesia breach of protocol, they were not excluded from the study. The Kahwaji et al. (1997) results are based on all subjects treated because analysis showed no difference among the "all subject treatment" group, the "per protocol" group (with violations excluded), and the "intent to treat" group in which patients were assigned to the original randomized dose. A total of 120 younger adult and 58 elderly patients were evaluated. Kahwaji et al. (1997) organized their findings by age group and dose given. A 95% confidence interval was used with a p value < 0.05 considered statistically significant. The younger adult group received an excellent or good intubation score at 60 or 90 seconds for 80 of the patients. The 40

patients who fell below excellent or good included 19 who received a placebo, 11 who received 0.5mg/kg, five who received 1.0mg/kg, 4 after 1.5mg/kg, and one after receiving 2.0mg/kg. The elderly group documented 34 patients receiving an intubating score of excellent or good. The remaining elderly group members who received below good included 10 who received a placebo, seven after 0.5mg/kg, four after 1.0mg/kg, two after 2.0mg/kg, and one after receiving 2.5mg/kg.

Twenty-three adverse experiences were reported in 16 patients. Two of these events (tachycardia, with heart rate from 85 to 150 beats per minutes, and bronchospasm) met the criteria for serious adverse effects. Dose-dependent changes were observed in tracheal intubating conditions and neuromuscular block. The demographic comparison showed that there were no differences in weight, height, and age among the six dose groups in the elderly and young adult age groups. Mean duration of less than 20 minutes was observed in the younger adults at doses up to 2.0 mg/kg and in the elderly at up to 1.5 mg/kg. Although the recovery times for the elderly patients were longer than the younger adult patients, the result showed no statistically significant differences in clinical duration between the younger adult and elderly patients at any treatment dose of rapacuronium. Thus, doses of 1.5 – 2.0 mg/kg rapacuronium enabled both rapid tracheal intubation and a short clinical duration of action in adult and elderly patients (Kahwaji et al., 1997)

The Kahwaji et al. (1997) study confirmed the rapid onset of neuromuscular block in adults after rapacuronium provided conditions for rapid tracheal intubation and a short clinical duration of action at 1.5 – 2.0 mg/kg. Rapacuronium is a rapid-onset (1-2 minutes), short (8-20 minutes) or intermediate (20 – 50 minutes) clinical duration, neuromuscular-blocking drug. Kahwaji et al. stated that a dose of rapacuronium 1.5-

2.0mg/kg would provide the fastest onset of actions for rapid intubation of all patient groups. One shortcoming of this study was that comparisons were not made with existing drugs with equipotent doses; although based on their review of literature, the authors found that the dose-dependent duration of action was similar to that of atracurium, cisatracurium, vecuronium, and rocuronium.

Rocuronium has been on the market for several years prior to the introduction of rapacuronium. Heier and Caldwell (2000) provide a look at rocuronium's neuromuscular blockade effects for rapid tracheal intubation. A sample size of 60 patients, ASA class I and II, ages 18 – 55years, receiving an elective procedure were utilized. Exclusion criteria included individuals with greater than 30% of their ideal body weight, those on medications that could interfere with neuromuscular transmission, or those who have a neuromuscular disorder. Premedication consisted of midazolam. Induction agents used included alfentanyl, thiopental, and administration of one of five doses of rocuronium. Patients were randomly chosen to receive either 0.4, 0.8, 1.2, 1.6, or 2.0mg/kg of rocuronium. After tracheal intubation was accomplished, maintenance of isoflurane or desflurane with intermittent doses of fentanyl was given. Nerve stimulation was accomplished at the ulnar nerve using TOF. Rocuronium's duration of action was measured by the time difference from administration until return of twitch response. TOF was evaluated every five minutes post administration. Changes in heart rate and systolic blood pressure also were documented.

Intubation was evaluated by developed criteria for excellent, good, and poor conditions. All patients were intubated within 60 seconds. However, not all patients were given an excellent intubation rating at the time of intubation due to movement at the

diaphragm. Heier and Caldwell (2000) found that rocuronium 2mg/kg would produce a 90% or greater probability for success in rapid sequence intubation. However, the authors considered this dose to be large. An appropriate dose range of rocuronium for tracheal intubation is 0.9 – 1.2 mg/kg (Saverese et al., 2000). The authors also found that there was an increase in the duration of action with an increased dose of rocuronium. A dose of 2.0mg/kg was documented to last a median period of close to two hours. Systolic blood pressure and heart rate did increase by 20% or greater in 68% of the patients, but was not correlated to any specific dose. Heier and Caldwell do not recommend large doses of rocuronium for intubation due to the potential compromise to patient safety when the airway has not been secured.

Comparison to Other Neuromuscular Blocking Agents

The introduction of rapacuronium provided the medical community with another nondepolarizing agent to test against succinylcholine. It promises fast onset and short duration of action without the undesirable histamine release that makes steroidal compounds an attractive alternative (Saverese et al., 2000).

Wierda and colleagues (1993) compared rapacuronium to succinylcholine. A sample size of 45 patients, ASA class I-III, ranged in age from 18 – 65 years, scheduled for elective surgery were studied. No exclusion criteria were given. Patients were randomly assigned to one of three groups of 15 patients each: Group A received succinylcholine, Group B received rapacuronium reversed with neostigmine, Group C received rapacuronium without reversal.

All patients in the (Wierda et al., 1993) study were premedicated with midazolam. Induction agents used were fentanyl and thiopental. Maintenance included 1%

isoflurane, 67% N2O and O2 mixture, and fentanyl. End tidal CO_2 and temperature was controlled so consistency among all patients could be established. A baseline response to single twitch at the adductor pollicis was determined and TOF was monitored after administration of the neuromuscular blocking agents for each group. Single twitch contractions of adductor pollicis muscle at preload of 200 – 400 grams were measured with a Relaxometer after induction of anesthesia. A force displacement transducer quantified the force of thumb adduction. Single twitch contractions at 0.1 Hertz were recorded at least five minutes after administration of the relaxant. TOF stimulation was started after the relaxant, and was continued until maximum recovery of response was obtained for succinylcholine. TOF was monitored until 70% recovery for rapacuronium. Two minutes after administration of rapacuronium, Group B received neostigmine for reversal. Intubating conditions were measured by an attempted intubation following the first minute after administration of either succinylcholine or rapacuronium. If unsuccessful, another attempt was made at the end of the second minute. One anesthesiologist performed the laryngoscopy for all patients.

Statistical analysis of differences among the three groups was conducted using ANOVA, x^2 test, unpaired Student's *t*-test, or Wilcoxon rank sum test, depending on the type of data being analyzed. A p value of < 0.05 was considered significant. Results were not statistically significant. All but one of the patients (Group A) could be tracheally intubated at one minute under good to excellent conditions. Endotracheal intubation conditions also were similar after both muscle relaxants. All but one patient was intubated one minute post-administration. Onset time for rapacuronium was similar to succinylcholine and was not clinically significant. Duration of action was noted as

shorter in Group B. Group A and C required a mean of eight minutes for a single twitch response of 25% recovery. Group B documented 5.7 minutes to a single twitch of 25% recovery. Most significant was the difference in duration between Group B and Group C for TOF recovery response to 70%. Group C experienced a mean duration of 24.1 minutes. Group B recovered 70% TOF response at approximately 11.6 minutes (Wierda et al., 1993).

Rapacuronium produced a neuromuscular blockade with fast block development and good to excellent intubating conditions one minute after its administration. Combined with neostigmine given two minutes after rapacuronium, duration until sufficient clinical recovery of rapacuronium induced neuromuscular block was found to be similar to that of succinylcholine. Wierda et al. (1993) advocate this finding to be very important when using rapacuronium for intubation, because recovery of 24 minutes could be fatal if an airway cannot be secured immediately. The use of neostigmine can increase its safety margin. The authors concluded that rapacuronium (with neostigmine given as a reversal agent) is suitable for endotracheal intubation and short-lasting interventions (Wierda et al.).

Schiere, van den Broek, Proost, Molenbuur, and Wierda (1997) compared the interaction of rapacuronium with vecuronium in a study of 60 patients. Volunteers were categorized as ASA class I and II, and undergoing elective surgical procedures of approximately 60 minutes in duration. Exclusion criteria included individuals with known neuromuscular, renal, or hepatic disease, and anyone receiving medication that could interfere with neuromuscular transmission. Patients were randomly categorized into one of four groups: (a) Group 1 received rapacuronium for induction and

maintenance; (b) Group 2 received rapacuronium for induction and vecuronium for maintenance; (c) Group 3 received vecuronium for induction and maintenance; (d) Group 4 received vecuronium for induction and rapacuronium for maintenance.

Induction agents used were thiopenthal and fentanyl. Maintenance included fentanyl, halothane, and a 2:1 mixture of N2O and O2. End tidal CO2 and temperature were maintained within normal limits. Single twitch response at the ulnar nerve was established prior to administration of neuromuscular blocking agents and TOF was used after administration. The initial dose given of rapacuronium and vecuronium was 1.5 mg/kg and 0.07 mg/kg, respectively. Maintenance doses included rapacuronium 0.55 mg/kg and vecuronium 0.025 mg/kg. The Wilconon rank sum test, Kruskal-Wallis test, Dunn test, and Fisher exact test were used for statistical analysis and a p value < 0.05 was considered significant (Schiere et al., 1997).

Duration of block for the group receiving an initial dose of rapacuronium followed by vecuronium was shorter than those receiving vecuronium as an initial relaxant ($p < 0.001$). The shortest duration of action was noted when rapacuronium was given as the initial and maintenance neuromuscular blocking agent (Schiere et al., 1997). This finding is an advantage because it increases the flexibility of the drug for short surgical procedures. The most prominent finding reported was no clinically significant difference in the duration of action of maintenance vecuronium when either rapacuronium or vecuronium were given initially. Shiere et al. offered an explanation that the maintenance dose was given while the receptors were still greater than 80% occupied by the initial agent. The removal of the initial dose of neuromuscular blocking agent from the receptors must occur before affects of the maintenance drug can be seen. Another

explanation is the idea of synergism versus added effects. This idea suggests that chemically unrelated drugs provide synergistic effects and chemically related drugs provide additive effects to subsequent dosing. Shiere et al. conclude that rapacuronium is a suitable choice for intubation and maintenance of short surgical procedures lasting less than one hour.

In a multi-center investigation, Sparr, Mellinghoff, Blobner, and Noldg-Schomburg (1999) studied 335 patients undergoing elective surgery to compare the intubating conditions provided by rapacuronium given at a 1.5 mg/kg dose versus succinylcholine given at 1 mg/kg dose, after rapid sequence induction of anesthesia. The patients were between 18 to 65 years of age, with an ASA physical status classification of I and II. They were randomly assigned to one of four treatment groups that differed in the neuromuscular blocking agent (rapacuronium and succinylcholine) and in the induction technique (thiopenthal with fentanyl or propofol with alfentil). None of the patients in the study were taking any medication that could have interacted with neuromuscular blocking agents, nor did any of them have a history of malignant hypothermia. All particiapants received standard protocol premedication. One fully trained anesthetist in each center, blinded to each patient treatment, performed all intubations at 50 seconds. Five factors were considered for assessment: (a) ease of laryngoscopy, (b) position of the vocal cords, (c) movement of the vocal cords, (d) movement of limbs, and (e) airway reaction. The onset of the block was not measured because the authors felt that maintaining anesthesia necessary during stabilization of twitch response interfered with assessing intubating conditions after rapid sequence induction.

All quantitative variables were calculated for each group using two-sided 95 percent CI, the Mantel-Haenszel test, two way repeated measures ANOVA, or Student's *t*-test depending on the type of data being analyzed. Nineteen patients were excluded from the study due to protocol violations (pregnancy, n = 1; paravenous injection, n = 1; incorrect induction technique, n = 4; incorrect body mass index, n = 5; incorrect neuromuscular blocking agent dose, n = 8). In 89.4 percent (n = 143) of the rapacuronium patients, intubating conditions were clinically acceptable (good to excellent), while 97.4 percent (n = 152) were clinically acceptable in the succinylcholine patients (p = 0.004; 95 percent CI, 2.0 – 14.1%). The maximum increase in the heart rate averaged 23.1 percent (SD, 25.4) after rapacuronium, and 9.4 percent (SD, 26.1) after succinylcholine (p <0.001). About 10% of the sample intubated with rapacuronium experienced pulmonary side effects while only 4% of those receiving succinylcholine experienced these side effects. The results of the study showed clinically acceptable intubating conditions can be achieved with rapacuronium 1.5 mg/kg (Sparr et al., 1999).

Wright, Caldwell, and Miller (1994) evaluated a range of doses likely to be used for tracheal intubation (0.4mg/kg – 1.2mg/kg) of rocuronium to determine rate of onset and magnitude of neuromuscular blockade at the laryngeal adductor and adductor pollicis muscle compared with succinylcholine (1mg/kg). A total of 48 subjects, 18 – 70 years old, ASA physical status I – III undergoing greater than two hour surgical duration were randomly selected to receive one of three doses of rocuronium (0.4, 0.8, or 1.2 mg/kg) or succinylcholine (1mg/kg). Each group studied had 12 patients. Propofol and fentanyl were used for induction and maintenance. Muscle relaxants were not used to intubate. Neuromuscular transmission was monitored at the adductor pollicis and the laryngeal

adductor muscles by mechanomyography. Pressure changes in the inflatable cuff of the endotracheal tube, due to the evoked force of vocal cord adduction, were detected using a pressure transducer. After administration of the pre-determined rocuronium dose, supramaximal TOF sequence was evoked every 12 seconds to the anterior branch of the recurrent laryngeal nerve and the ulnar nerve until T1 had recovered to a minimum of 25% control at both muscle groups; and until T1 recovery was complete with succinylcholine.

The variables assessed were lag time (time to first depression of T1), onset time (time to maximum block or 12 seconds after detectable twitch when 100% twitch depression occurred), peak effect (maximum T1 depression), and time until T1 recovered to 25% of its control value (control value was the amplitude of the first response, T1). One shortcoming identified by the authors was that they did not evaluate intubation conditions. Paired-sample *t*-test compared muscle groups within a drug group. ANOVA was used to assess the effect of rocuronium dose on lag time, onset, time, peak effect, and time to 25% recovery of T1 at each of the muscle group. ANOVA with Dunnett's test was used to compare onset, duration variables, and peak effects to the three groups of rocuronium and succinylcholine and a $p < 0.05$ was used to determine statistical significance (Wright et. al, 1994).

Wright et al., (1994) reported that peak effect at the laryngeal adductors exceeded 99% in all patients given succinylcholine and none (0%) given 0.4mg/kg, five (42%) given 0.8mg/kg, and ten (83%) given 1.2mg/kg of rocuronium. Peak effect at the adductor pollicis exceeded 99% in all subjects except two subjects who received 0.4mg/kg rocuronium (peak effects 91% and 97%). Onset time was significantly more

rapid at the laryngeal adductors than at the adductor pollicis with succinylcholine and rocuronium 0.4mg/kg. The result was explained by considering the relationship between the dose and onset time at muscles with differing sensitivity. Onset time was similar at the two muscle groups with 0.8mg/kg and 1.2mg/kg of rocuronium. Wright et al. theorized that large doses of rocuronium might shorten the onset time at the larynx, but would also prolong the duration of action. The larynx measurement showed more variation and interference than at the adductor pollicis. The study showed that the duration of effect of rocuronium was 20 – 30 minutes less at the larynx than at the adductor pollicis; similary, succinylcholine, had a shorter duration of action at the larynx (6 – 8 minutes) than at the adductor pollicis (10 – 12 minutes). Wright et al. concluded that the duration of complete relaxation at the laryngeal muscles is only half of that indicated at the adductor pollicis. Their findings suggest that a replacement drug for succinylcholine must possess the pharmacokinetic ability to be given in very large doses without prolonged duration of action.

Summary

Rapacuronium is a short-acting, nondepolarizing agent suitable for rapid intubation and for short surgical procedures. Rocuronium, belonging to the same class of aminosteroid compounds as rapacuronium, is an intermediate acting nondepolarizing agent with a slower onset of action. A comparison to the combination of rapacuronium and rocuronium is important to the understanding of the usefulness of this relatively new drug. Findings from studies using rapacuronium as a neuromuscular blocking agent have demonstrated that it has the potential to replace succinylcholine as the drug of choice for rapid sequence intubation due to its rapid onset and equilibration.

CHAPTER III: METHODS

Research Design

An experimental research design was used in this study. The essential elements for an experimental study design include: random sampling, researcher manipulation of the independent variable, and a control or usual treatment groups for comparison (Burns & Grove, 1997). Each element listed above was employed in the execution of this study. Volunteers, meeting the inclusion criteria, were randomly assigned to one of two groups: (a) Group A received succinylcholine and rocuronium; (b) Group B received rapacuronium and rocuronium. The independent variable was the drug combination received. Succinylcholine and rapacuronium, dosage was closely controlled for each volunteer; they received a determined set dose for their body weight of each neuromuscular relaxing agent. The dependent variable was the response noted via nerve stimulation, which was assessed using the TOF. Standard premedication agents included midazolam and fentanyl. Induction anesthetic agents given were propofol and sevoflurane. Equipment to ensure valid measurement of the dependent variable will be discussed under measurement methods.

Sampling and Setting

A record review of potential volunteers was completed and an initial interview done by the investigators to ensure that the volunteers met the inclusion criteria. Volunteers were recruited during pre-operative anesthesia interview. Volunteers were given information regarding the study with ample time to ask questions for clarification. Once recruited, volunteers were randomly assigned to one of two groups: (a) Group A received succinylcholine 1.0 mg/kg as the intubating agent, and rocuronium 0.3 mg/kg as

the maintenance agent; (b) Group B received rapacuronium 1.5 mg/kg as the intubating agent, and rocuronium 0.3 mg/kg as the maintenance agent. Randomization was accomplished by writing the numbers 1 through 30 on individual pieces of folded paper. The anesthesia provider drew from the numbers. The numbers 1 through 15 were assigned to Group A, and numbers 16 through 30 were assigned to Group B. A sample size of 15 volunteers in each group was needed for an alpha of $p = 0.05$ and a power of 0.80.

Inclusion criteria were: (a) volunteers between the age of 18 – 65 years, (b) an assigned ASA classification of I – III, and (c) planned elective surgical procedures requiring general endotracheal anesthesia lasting at least one hour in length. All volunteers were English-speaking and included both genders to increase the generalizability of the results. Exclusion criteria were: (a) those with allergies to neuromuscular blocking agents, (b) those with a family history of malignant hyperthermia, (c) those undergoing treatment for neuromuscular disorders, (d) those with severe cardiovascular, respiratory, liver, or renal disease, (e) those on prescribed medications that may interfere with neuromuscular transmission (such as aminoglycosides, organophosphates), (f) those who were pregnant, and/or (g) those anticipated to have a difficult airway. A difficult airway was defined as Mallampati classification III or IV, patients over 20% ideal body weight, patients diagnosed with rheumatoid arthritis, obstructive sleep apnea, or prior surgery/radiation therapy for head or neck cancer.

Data were collected at a single medical center located in a major west coast metropolitan city. This facility has approximately 300 inpatient beds. It has eight

operating room suites and supports 4800 anesthesia procedures per year, and with 5,200 admissions, and 245,300 outpatient visits yearly. This medical center provides a full range of medical and surgical services, excluding open-heart surgery and organ transplantation. Data collection started in December 2000 and concluded in March 2001. Two graduate student nurse anesthetists were the principal investigators and conducted the data collection.

Measurement Methods

Appendix A contains the tool used for data collection. All subjects received a standard premedication dose of Versed 1 – 2mg, Fentanyl 100 – 150 mcg, and an induction dose of Propofol 1.5 – 2.5 mg/kg. Maintenance of anesthesia was carried out with Sevoflurane at 1.0 MAC. Neuromuscular monitoring was started at induction to allow for calibration and stabilization. Once unconsciousness was confirmed, neuromuscular blockade was monitored using the Paragraph™ Peripheral Nerve Stimulator, an accelerometer. The piezoelectric sensor measured the force (acceleration) generated by the thumb when electrically stimulated (Orr, Westenskow, & Dwayne, 1996). The adductor pollicus was monitored via the ulnar nerve. Placement of the stimulation pad (larger pad) was placed parallel to the ulnar nerve at the wrist. The motion sensor pad (smaller pad) was placed on the distal metacarpal joint of the thumb perpendicular to the natural creases on the hand. The pad detects the number and strength of muscle twitches (Kern, Johnson, Westenskow, & Orr, 1994). Maximal twitch height was established prior to administration of neuromuscular relaxants. The milliampereage was then increased by 10 to provide supramaximal stimulation. Supramaximal stimulation was continued for remainder of observation. Group A

received succinylcholine 1.0 mg/kg for induction. Group B received rapacuronium 1.5 mg/kg for induction. All subjects received rocuronium 0.3 mg/kg as the maintenance neuromuscular blocking agent.

The following variables were measured and recorded: (a) time rocuronium maintenance dose given, (b) return of the first twitch after the first maintenance dose of rocuronium, and (c) return of the second twitch after the first maintenance dose of rocuronium. Upon recovery of the second twitch, the data recording was concluded.

Protection of Human Rights

All participants in the study were volunteers. Each subject received a standardized explanation of the study, opportunity to ask the investigators specific questions regarding the purpose, and administration of the study. Informed consent was obtained following USUHS requirement and local policy. A copy of the consent form is in Appendix B. Subjects received a copy of the consent upon discharge from the pre-operative anesthesia interview. No names or other identifying information were recorded for public knowledge. The data collection tool did not include the volunteer's name, hospital number, or social security number.

Data Analysis

The Statistical Package for the Social Sciences (SPSS) 2000 was used for data analysis. An independent sample *t*-test was executed to compare the two study groups. Data were reported as individual values; a $p \leq 0.05$ was considered statistically significant.

CHAPTER IV: STUDY FINDINGS

Findings

The sample consisted of 15 males and 15 females, with a mean age of 34.2 years. There were 19 ASA Class I and 11 ASA Class II. No ASA Class III subjects were obtained in the sample. The sample was randomly allocated into two groups of equal size. Group A received succinylcholine and rocuronium. Group B received rapacuronium and rocuronium. There were no adverse side effects experienced by the subjects in the groups.

An independent sample *t*-test was performed to compare the duration of time until the second twitch (in minutes) for different drug types (rapacuronium versus succinylcholine). Although the time until the second twitch was numerically shorter in Group A (26.87 minutes) compared to Group B (36.20 minutes), these differences were not statistically significant ($p = 0.111$) between the two groups as seen in Figure 1.

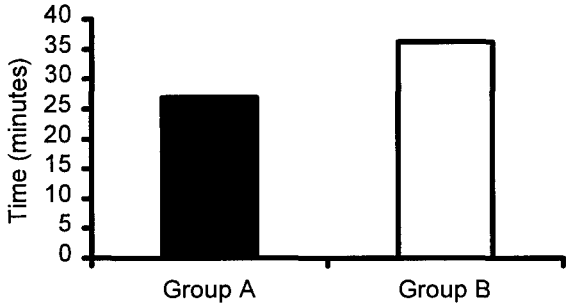

FIGURE 1
Induction Group
Return of Second Twitch Following Maintenance Dose of Rocuronium

The time of return of the first twitch was also noted. In the succinylcholine group (Group A), six subjects maintained one twitch after the maintenance dose of rocuronium. Only two subjects within the rapacuronium group (Group B) maintained one twitch after

receiving the maintenance dose of rocuronium. The duration of time until the return of the first twitch (including the subjects that did not lose all twitches) in the succinylcholine group was 16 minutes, as compared to 31.2 minutes within the rapacuronium group (Figure 2).

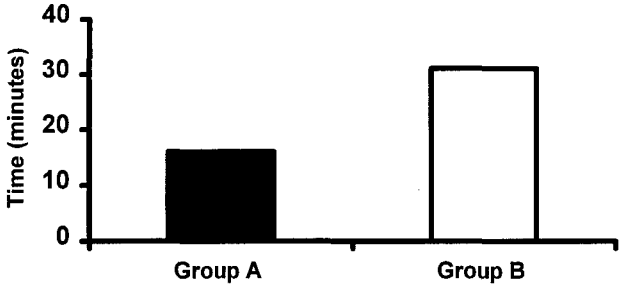

FIGURE 2
Induction Group

Return of First Twitch Following Maintenance Dose of Rocuronium

Since an inhalational agent may influence neuromuscular blocking agents (Donnelly, et. al, 1999) the end-tidal percent of sevoflurane was documented for each subject. The mean percent end-tidal in the succinylcholine group was 2.20 MAC. The mean percent end-tidal in the rapacuronium group was 1.95 MAC. This difference was not statistically significant (Figure 3).

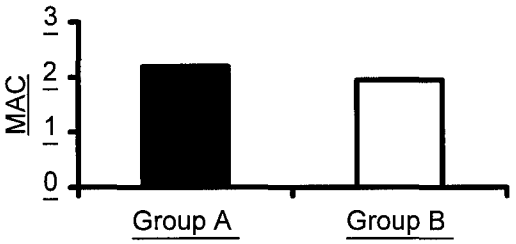

FIGURE 3
Induction Group

Percent End-Tidal of Sevoflurane

CHAPTER V: CONCLUSIONS AND RECOMMENDATIONS

The purpose of this study was to determine the effects of rapacuronium and succinylcholine on the duration of action of rocuronium. The 30 subjercts each received midazolam 1.0 – 2.0 mg intravenous prior to induction, fentanyl 100 – 150 mcg and propofol during induction. Sevoflurane with oxygen was the inhalation agent used, with no nitrous oxide added. Group A received succinylcholine for induction; Group B received rapacuronium for induction. Both groups received rocuronium as the maintenance neuromuscular blocking agent.

An independent samples *t*-test was performed to compare the duration of time until the return of the second twitch among the two study groups. The mean duration of time until the return of the second twitch within the succinylcholine group (Group A) was 26.87 minutes. The mean duration of time until the return of the second twitch with the rapacuronium group (Group B) was 36.20 minutes. These differences were not statistically significant ($p = 0.111$).

A mean time difference for return of the second twitch between the two groups was 9.33 minutes and could be clinically significant in terms of extra drug dosing and subsequent cost. The investigators noted the time to return of the first twitch. Among Group A, six subjects maintained one twitch after rocuronium was given. The mean duration of time (including the six subjects who did not lose all twitches) was 16 minutes. Among Group B, two subjects maintained one twitch after rocuronium was given. The mean duration of time (including the two subjects who did not lose all twitches) was 31.2 minutes. These findings do not support an earlier study by Savarese et al., (2000) which stated that the use of short-acting nondepolarizer followed by a maintenance dose of an

intermediate-acting nondepolarizer produced a shorter duration of action of the maintenance dose. However, in the present study, the large difference between the two groups in relation to the return of the first twitch may have clinical implications regarding reversal. Reversal of neuromuscular blockade requires a minimum return of one twitch to predictably achieve antagonism. Operative time would be prolonged while waiting for return of neuromuscular function. Prolonged operative time also increases the time the patient is exposed to the risks of anesthesia. Reversal without twitch return of neuromuscular function may in-turn prolong neuromuscular blockade (Longnecker, Tinker, & Morgan, 1998).

One limitation of the current study was the monitor used for data collection. The Paragraph™ Nerve Stimulator is an accelerometer, though it provides a visual screen display of the evoked mechanical responses, the time to 25% and 75% recovery could not be quantified. The investigators felt that these measurements could have yielded more definitive data. Another limitation of the monitor was fact that the particular stimulators used did not provide a printed graph measurement. Therefore, measurements presented on the visual display were left to interpretation by the investigators.

Another limitation was the use of study subjects who were not representative of the general population. Most of the volunteers included in the study were healthy. Recommendations for future studies include using the same research question but increasing the sample size, including patients who are within 30% of their ideal body weight, and using a mechanomyographer to measure neuromuscular response.

However, since rapacuronium was voluntarily removed from the market as of April 2001 due to three documented fatal bronchospasms, this study cannot be replicated. An

alternative might be to use succinylcholine and rocuronium, with vecuronium as the maintenance agent, to find out if the action of vecuronium can be potentiated.

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APPENDICES

APPENDIX A

Subj #	Age	Gen der	ASA	Induction start time	Initial dose	Onset time	Time roc given	Return first twitch	Time in min from dose of roc	Return second twitch	Time in min from dose of roc	Side effects/ Adverse effects	Max twitch heighth + 10	Fentanyl dose (mcg)	% Sevo MAC

Appendix B

60TH MEDICAL GROUP
David Grant Medical Center
101 Bodin Circle
Travis AFB, CA 94535-1800

Privacy Act of 1974 applies. DD Form 2005 filed in Clinical/ Medical Records.

PRIVACY ISSUES: *Records of my participation in this study may only be disclosed in accordance with federal law, including the Federal Privacy Act, 5 USC 552a, and its implementing regulations. DD Form 2005 contains the Privacy Act Statement for the records. I understand that records of this study may be inspected by the U.S. Food and Drug Administration (FDA), the sponsoring agency and/or their designee, if applicable.*

Capt(s) Rachael Fontanilla and Virginia Johnson, NAR, Anesthesia Department (707)423-3590
Maj. Sylvia Cayetano, Clinical Director, Nurse Anesthesia Program, DGMC (707)423-3590

TITLE OF STUDY

"The Effect of Rapacuronium or Succinylcholine on the Duration of Action of Rocuronium"

INVESTIGATORS' NAMES, DEPARTMENTS, PHONE NUMBERS

INTRODUCTION

I am being invited to take part in a research study being conducted by the nurse anesthesia program at the Uniformed Services University of the Health Sciences in conjunction with David Grant USAF Medical Center, (DGMC). It is important that I read and understand several general principles that apply to all who take part in research studies: (a) taking part in the study is entirely voluntary; (b) personal benefit may not result from taking part in the study, but knowledge may be gained that will benefit others; (c) I may withdraw from the study at any time without penalty or loss of any benefits to which I am otherwise entitled. The nature of the study, the risks, inconveniences, discomforts, and other pertinent information about the study are discussed below. If I have personal, religious or ethical beliefs which I think might limit the types of medical treatment (for example, blood transfusions) that I would agree to receive, I should discuss them fully with my physician(s) before entering this study. I am urged to discuss any questions I have about this study with my anesthesia provider(s).

PURPOSE OF STUDY

(This section will explain the nature, purpose(s), approximate number of subjects, and the duration of participants' involvement.)

I, _____ (SSN: ___ - ___ - ____), understand that I am being asked to participate in a research study.

The Department of Nurse Anesthesia of the Uniformed Services University of the Health Sciences is carrying out this research study with DGMC to find out whether rapacuronium and succinylcholine will have an effect on the duration of action (the amount of time the drug will work) of rocuronium (medicines that relax muscles). I will be one of 30 volunteers asked to participate in this research study. If I choose to volunteer for the study, I will be randomly assigned to one of two treatment groups. Randomization means I will be chosen to either Group A or Group B by my anesthesia provider, selecting a number at random from 1-30. Group A will receive rapacuronium as the induction agent (medicine that will relax your muscles) and rocuronium as the maintenance agent (keeps my muscles relaxed). Group B will receive succhinylcholine as the induction agent and rocuronium as the maintenance agent. The time commitment for this study will be the first hour of my surgery. There will be no additional time required. The entire length of the study will be two weeks for gathering data.

PROCEDURES

The procedure for this study includes giving me anesthesia medications needed to put me to sleep. All medications in this study are useddaily in providing general anesthesia at this facility. My anesthesia provider will choose the appropriate medications to administer according to my surgery, including but not limited to anxiolytic (medicine to reduce anxiety), narcotics (medicine to reduce pain), and induction agents (medications to put me to sleep). The study will be conducted as followed. I will be randomly assigned to Group A or B. If assigned to Group A, I will be given rapacuronium 1.5 mg/kg and rocuronium 0.3 mg/kg. If assigned to Group B, I will be given succinylcholine 1.0 mg/kg and rocuronium 0.3 mg/kg. My anesthesia provider will administer standard medications needed for surgery. Rapacuronium or succhinylcholine will be given to relax my muscles. My muscle response will be monitored using a peripheral nerve stimulator. This is standard procedure when muscle relaxants have been given. My muscle response will continue to be monitored until recovery from the medicine. This information will be recorded on a data collection sheet. The results from thestudywill be based on the information collected on the data sheet.

(This section will explain all procedures and the purpose of the procedures to be undergone as part of this study. Any experimental procedures will be explained as such.)

BENEFITS

There is no direct benefit to participating in this study. However, results observed during the conduct of this study will help further understanding of routine anesthetic medications for improvement in clinical practice.

ALTERNATIVES

(This section will explain your alternative treatment possibilities)

The alternative is to not participate in this research study. I will then be treated with standand medications deemed appropriate by my anesthesia provider.

RISKS/INCONVENIENCES

(Any discomfort , risks, inconveniences caused from procedures or drugs used that may be expected from participation in this study.)

I am not incurring any greater risk from participating in this study than I would receive from general anesthesia for my surgery. These drugs are commonly used in this facility.

EVENT OF INJURY

I understand that my entitlement to medical and dental care and/or compensation in the event of injury is governed by federal laws and regulations, and if I have questions about my rights or if I believe I have received a research-related injury, I may contact the 60th Medical Group (DGMC) Patient Relations Monitor, at (707)423-3729, the Director of the Clinical Investigation Facility at (707)423-7400, and/or the investigator, Capt(s) Rachael Fontanilla and Virginia Johnson at (707)423-3590. I may also contact the medical monitor Lt Col Mary Nelson at 423-7262.

OCCURRENCE OF UNANTICIPATED EVENT

If an unanticipated event (clinical or medical misadventure) occurs during my participation in this study, I will be informed. If I am not competent at the time to understand the nature of the event, such information will be brought to the attention of my guardian or next of kin.

DECISION TO PARTICIPATE

The decision to participate in this study is completely voluntary on my part. No one has coerced or intimidated me into participating in this program. I am participating because I want to. My investigator(s) has adequately answered any and all questions I have about this study, my participation, and the procedures involved. I understand that the investigator will be available to answer any questions concerning procedures throughout this study. I understand that if significant new findings develop during the course of this study that may relate to my decision to continue participation, I will be informed. I further understand that I may withdraw this consent at any time and discontinue further participation in this study without prejudice to my entitlement to care. I also understand that the investigator of this study may terminate my participation in this study at any time if he/she feels this to be in my best interest. I have been provided a copy of this consent form.

My signature below indicates my willingness to participate in this research study.		
_____ (Subject's Printed Name)	_____ (Subject's SSN)	
_____ (Subject's Signature)	_____ (FMP* & Sponsor's SSN)	_____ (Date)
_____ (Advising Investigator's Signature)	_____ (Investigator's SSN)	_____ (Date)
_____ (Witness's Signature)	_____ (Witness's SSN)	_____ (Date)

Distribution:
(1) Clinical Investigation Facility (60MDSS/SGSE); [original]
(2) Research Volunteer;
(3) Volunteer's Outpatient Medical Record, (permanently maintained);
(4) Principal Investigator.

* FMP (Family Member Prefix) such as 20 - sponsor, 30 - dependent spouse, 01 - first child, etc...)